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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/042,460	03/16/98	MORIN G	015389003110

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	35

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/042,460	MORIN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,22-26 and 28* is/are rejected.

7)☒ Claim(s) *21 and 27* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

The applicant's response filed on Paper No. 22, 11/7/00 has been fully considered. Claims 29-30 are canceled. Claims 20 and 28 are amended. Claims 20-28 are pending and are examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/07/00 has been entered.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78). The applicants are required to update the status of "US App. No. 08/979,742 filed 11/26/97, now abandoned" in the first sentence of the instant specification.

Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: After applicant's amendment on 02/14/00 the instant application claims priority only to US App. No. 08/979, 742 filed 11/26/97, which is now abandoned and not to the other US or PCT applications as stated in the declaration. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. Claim 20, 23 and 26 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, **had possession of the claimed invention** and for the reasons of record set forth in Official action mailed 7/05/00.

Applicant's arguments filed on Paper No. 22, 11/07/00 (response, pages 3-5) have been fully considered but they are found unpersuasive. Citing the Written Description Guidelines (Fed. Reg. Dec 21, 1999, 64:71427-71440), the applicant argues that a claim drawn to a genus may be satisfied by disclosure or relevant identifying characteristics (response, page 4, para. 1). The applicant further argues that the phrase "has at least 90% sequence identity to SEQ ID NO:2" of the independent claim 20 provides substantial structural information about the members of the genus. Furthermore, the claimed genus recites that each encoded proteins must have "telomerase catalytic activity" (response, page 4, para. 2). The applicant further argues that

figure 4and 5 teaches substantial information about conserved motifs within the TERT protein sequence (response, page 4, para. 3). The applicant further argues that structural variation among members of the claimed species will not be great, since all members of the presently claimed genus must encode proteins with at least 90% homology to SEQ ID NO: 2 (response, page 5, para. 1).

However, this is not found persuasive for the same reasons of record as set forth in the official action mailed on 07/05/00. The instant claim is drawn to an isolated nucleic acid molecule encoding mTERT and its allelic variants with at least 90% sequence identity to amino acid sequences of SEQ ID NO:2. The invention as claimed encompass a polynucleotide, which encodes a mTERT wherein 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide. The variation also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase (mTERT) activity. At best the specification only discloses the nucleic acid encoding SEQ ID NO:2 having mTERT like activity and fails to disclose a single variants of SEQ ID No:2 that have mTERT like activity. As stated in the earlier office action, the general knowledge in the art concerning telomerase is that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998). The specification as filed fails to disclose common attributes of individual variants other than SEQ ID NO: 1 and 2. According to these facts, one skill in the art would conclude that applicant was not in the possession of the claimed genus because a description of only one member of this genus is not representative of the variants of genus and is insufficient to support the claim.

5. Claim 20, 23 and 26 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide encoding mTERT protein of SEQ ID NO:2, does not reasonably provide enablement for any and all variants that has at least 90% sequence identity to SEQ ID NO:2 and has telomerase catalytic activity when associated with a telomerase RNA. The specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims, for the same reasons of record as set forth in the official action mailed on 07/05/00.

Applicant's arguments filed 07/05/00 (pages 6-9) have been fully considered but they are found unpersuasive. The applicant argues that polynucleotide encoding mTERT protein vatients can be readily prepared with knowledge of one ordinary skill in the art without excessive trail and error experimentation. The applicant further argues that identification of conserved residues would have contributed to the skilled artisan's ability to predict which amino acid residues likely could be mutated without a loss of catalytic activity (response, page 4, para. 1-2, specifically para 2, line 10-12). The applicant further argues that the variants as claimed in claim 20 could be identified by screening mTERT activity using TRAP assay, which is well within routine experimentation (response, page 8, para. 1, line 8-11). The applicant further argues that polynucleotide sequences of the mTERT variant do not need to be predictable *a priori* for the present claim to be enabled.

However, this is not found persuasive for the same reasons of record as set forth in the official action mailed on 07/05/00 and as stated above. The instant claims are drawn to an isolated nucleic acid encoding a mouse TERT protein which has 90% sequence identity to SEQ ID NO: 2 and has telomerease activity. The specification as filed fails to disclose any and all polynucleotide sequences that has 90% sequence identity to SEQ ID NO: 2 and has telomerase like activity. The invention as claimed encompass a polynucleotide, which encodes a mTERT wherein 10% of amino acid sequences are added, deleted or substituted over the entire length of the polypeptide. The variation also encompasses the conserved motifs that are germane to the telomerase reverse transcriptase (mTERT) activity. At best the specification only discloses the nucleic acid encoding SEQ ID NO:2 having mTERT like activity and fails to disclose a single variants of SEQ ID No:2 that have mTERT like activity. As stated in the earlier office action, the general knowledge in the art concerning telomerase is that telomerase-complex consists of TERT protein, RNA component and other TRT associated proteins. Furthermore, TERT protein

consists of several conserved motifs that are required for the telomerase activity (Lundblad, PNAS 95:8415-8416, 1998, *ref of record*). The specification as filed fails to identify the functional attributes of individual variants other than SEQ ID NO: 1 and 2. It is general knowledge in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable. The recited SEQ ID NO(s) are simply compute-generated hypothesis because no biological function has been established. The mere identification of critical regions would not be sufficient, as the ordinary artisan would immediately recognize that the encoded polypeptide must assume the proper three-dimensional configuration to be active, which is dependent upon the surrounding residues. Therefore, Applicant has not presented enablement commensurate in scope with the claims.

6. Claims 23-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an **isolated cell** comprising the polynucleotide that encodes SEQ ID NO:2 in vitro, does not reasonably provide enablement for any cell comprising the polynucleotide that encodes SEQ ID NO:2 or its variant in vivo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

The scope of instant claim encompasses a cell that is transformed in vivo, therefore the invention as claimed falls in the realm of gene therapy. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations (Rosenberg et al, Science 287:1751, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997). It has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on

the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Although, the gene therapy holds much promise to come the success will only be achieved through continued rigorous research on the most fundamental mechanisms underlying gene delivery and gene expression in animals (Rosenberg, Science 287:1751, 2000). Considering the unpredictability in the gene therapy art one skill in the art would unable to exercise the invention as claimed without undue amount of experimentation. The amount of experimentation required would include making of any and all viral and non-viral vectors encoding mTERT nucleotide sequences and successful delivery of the vectors to the target cells that would lead to mTERT expression in vivo.

7. Claim 28 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention, for the same reasons of record as set forth in the official action mailed on 07/05/00.

Applicant's arguments filed 11/07/00 (pages 10-11) have been fully considered but they are not persuasive. The applicant argues that earlier office action mailed 10/13/99 acknowledge that the mTERT gene can be knocked out using homologous recombination. The applicant further argues that example-4 in the specification provides step by step instruction on how disrupt mTERT gene in a mouse cell. The applicant further argues that the phenotype of an mTERT knock out mouse cell as taught by the applicant is not unpredictable (response, page 10, para. 1). The applicant further argues that office action has provided no evidence or argument to support its assertion that the disruption of the mTERT gene in particular would be rare extreme case alluded by Rossant et al, where gene disruption would not produce the predicted out come (response, page 10, para. 2-3). The applicant further argues that Nikaidio et al report that tissue cells derived from the mTERT knock out mice lacked telomerase activity, therefore one ordinary skill in the art would have been able to use the mouse cell as claimed.

However, this is not found persuasive because the instant claim encompass not only an isolated mouse cell but also include a mouse cell derived from a transgnic mouse (which is non-elected subject matter, see office action 07/05/00, page 2) wherein the endogenous mTERT gene has been mutated. The earlier office action clearly states that the applicants fails to disclose even a single transfected cell wherein any and all components of telomerase complex have been knocked out by recombinant means and an exogenous mTERT gene have been transfected. At best example-4 teaches the electroporation of pmTERTKO vector in to WW6 ES cells but falls short of disclosing a single cell clone wherein the mTERT gene has been mutated (see example-4, page 114, line 27-31). Similarly, the specification discloses the injection of WW6 ES clones into C57BL/6 blastocytes, wherein the mTERT gene has been knocked out but fails to disclose a single founder animal exhibiting the required phenotype.

The state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. (Wood. Comp. Med. 50(1): 12-15, 2000, see page12). The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism

that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These epigenetic effects can dramatically alter the observed phenotype and therefore can influence or later the conclusions drawn form the transgenic or knockout models (Sigmund, Arterioscler. Throm. Vasc. Biol.20:1425-1429, 2000, see page 1425). Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene. (Kappel et al. Current Opinion in Biotechnology 3:558-553 1992; see page 550, col.1, para. 3-4, page 548, col.2 para.2). Considering the effect of a particular genetic construct the applicant fails to disclose any mouse cells wherein the endogenous mTERT gene has been mutated by using pmTERTKO vector. Furthermore, Nikaidio et al does not teach the use of pmTERKO vector to make the knockout transgenic mice at the time of filing of this invention. The earlier office action clearly states that the phenotype of targeted mutations by a homologous recombination have not always been as predicted from the knowledge of the nature of the gene product and its pattern of expression. (Rossant et al , Phil. Trans. R. Soc Lond. B. 339:137-254, 1993; page 71 col.2 par.2). The homologous recombination is rare event. Furthermore, the homologous recombination in ES cells and the successful implantation of ES in the blastocyte is considered highly unpredictable. In addition, the embryonic stem (ES) cells are very sensitive to culture conditions and have natural tendency to differentiate, giving rise to unstable genome. (Viville, in Transgenic Animals, Houdebine (eds), Harwood academic publishers, France. pp307-321, 1997).

Thus, considering the unpredictable nature of homologous recombination and transgenic art, and lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the claimed invention, without an excessive and undue amount of

experimentation. The quantity of experimentation required would include the functional characterization of all nucleotide sequence that has 99% identity to SEQ ID NO 2, and the role of deduced polynucleotide sequences as a telomerase activity. In addition, the undue experimentation required would include making mouse cells derived from a transgenic mouse wherein the endoghenous mTERT gene has been mutated by recombinant means.

Conclusion

No claims are allowed.

Claims 20, 22-26 and 28 are rejected

Claims 21 and 27 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten independent form including all of the limitation of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under 37 CFR § 1.121 *(http://www.uspto.gov)* and A CLEAN COPY OF **ALL** PENDING CLAIMS IS REQUESTED to facilitate further examination.

S. Kaushal,
PATENT EXAMINER
AU 1633